CARDIOVASCULAR MEDICINE

Acute coronary syndrome and chronic infection in the Cork coronary care case–control study

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Heart 2005;**91**:19–22. doi: 10.1136/hrt.2003.031799

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Accepted 26 March 2004

Objective: To examine the association between chronic infection and cumulative burden of infection and acute coronary syndrome.

Design: The 5C (Cork coronary care case–control) study was a community based case–control study. Patients and controls underwent a standard physical examination and had blood samples taken for serological analysis for *Helicobacter pylori* (IgG), *Chlamydia pneumoniae* (IgA, IgM, and IgG), cytomegalovirus (IgG), and herpes simplex virus types 1 and 2 (IgG).

Setting: Patients were recruited from four hospitals in Cork City and Mallow Town. Controls, individually matched on age and sex, were selected by incident density sampling from the same general practices as the referent case.

Main outcome measures: Age and sex adjusted and fully adjusted odds ratios for acute coronary syndrome by seropositivity and by increasing number of infections.

Results: Cases and controls did not differ significantly in seropositivity to *C pneumoniae*, cytomegalovirus, herpes simplex viruses, and *H pylori*. In unconditional logistic regression analysis adjusted for age, sex, waist to hip ratio, smoking, physical activity, alcohol consumption, and social class there was no evidence of an increasing risk for acute coronary syndrome with increasing burden of infection.

Conclusions: The findings do not support an association between specific infectious agents and acute coronary syndrome and do not provide evidence of a burden of infection effect.

Chronic infection has been proposed as a possible causative agent in the development of acute coronary syndrome.[1] Many pathogens have been implicated in the development of acute coronary syndrome including *Chlamydia pneumoniae*, cytomegalovirus, *Helicobacter pylori*, and herpes simplex virus (HSV) types 1 and 2.[2–5]

A recent meta-analysis of observational studies did not support the hypothesis linking specific microorganisms to acute coronary syndrome.[6] Similarly, promising preliminary findings from randomised controlled trials of antimicrobial agents have not been reproduced in more recent work.[7–9] More recently attention has broadened to include the burden of infection hypothesis, the concept that it is not one specific infection per se but the cumulative burden of infection that increases a person's risk of acute coronary syndrome.[10 11]

Diseases of the circulatory system, of which coronary heart disease is the largest component, account for 41% of deaths in Ireland, and Ireland has one of the highest rates of mortality for cardiovascular disease in the European Union.[12 13] Acute coronary syndrome, defined as acute myocardial infarction or unstable angina, is one of the most common reasons for emergency admission to hospital in Ireland.[14] The aim of this study was to examine the association between chronic infection, specifically seropositivity for *C pneumoniae*, cytomegalovirus, HSV types 1 and 2, and *H pylori*, and acute coronary syndrome and to assess the odds of acute coronary syndrome with increasing burden of infection.

METHODS

Design, participants, and methods of data collection

The 5C (Cork coronary care case–control) study was a community based case–control study. The study was carried out in four Cork area hospitals and 86 general practices in Cork and Kerry. The case group (n = 227) was recruited from consecutive patients aged between 35–74 years (inclusive) admitted with a first acute myocardial infarction or first event unstable angina, defined on the basis of standard World Health Organization criteria, to four Cork areas hospitals over a 26 month period.[15] Controls were matched by age (within five years) and sex and were selected by incident density sampling from the age–sex registers or practice lists of the general practices from which the cases were referred (86 practices). In the original study protocol, the study had a power of 90% to detect an odds ratio of 2 for the association between *C pneumoniae* and acute coronary syndrome (assuming a *C pneumoniae* seropositivity of 50% in controls and a sample size of 300 cases and 600 controls). The power of the study was recalculated based on the achieved sample size and the power was 80% to detect an odds ratio of 1.7 for the association between *C pneumoniae* and acute coronary syndrome.

Exclusion criteria

The following characteristics were exclusion criteria for the study: (1) age < 35 years or > 74 years; (2) documented history of previous myocardial infarction, angina, other heart disease or stroke; (3) previous (old) 12 lead ECG showing pathological Q waves, ST segment deviation, T wave inversion, bundle branch or atrioventricular block, or tachyarrhythmia other than isolated extrasystoles; (4) documented coagulation disorder or myeloproliferative

Abbreviations: 5C, Cork coronary care case–control; ACADEMIC, azithromycin in coronary artery disease: elimination of myocardial infection with chlamydia; BRHS, British regional heart study; CI, confidence interval; EIU, enzyme immune units; ELISA, enzyme linked immunosorbent assay; HSV, herpes simplex virus; ISAR-3, intracoronary stenting and antithrombotic regimen; ROXIS, randomised trial of roxithromycin in non-Q-wave coronary syndromes; STAMINA, South Thames trial of antibiotics in myocardial infarction and unstable angina; WIZARD, weekly intervention with Zithromax for atherosclerosis and its related disorders

disease; (5) severe mental or physical disability; (6) severe or life threatening intercurrent illness; (7) residence outside the Southern Health Board area; (8) unwillingness to participate in the study; and (9) no contact telephone number. The same exclusion criteria applied for patients and controls. Patients were interviewed, examined, and had blood samples taken between 3–10 days after admission. Forty nine per cent of the age and sex matched controls were examined within one month of the patients (median 33 days, range 1–417 days).

Questionnaire and physical measurements

The questionnaire was adapted from the BRHS (British regional heart study) baseline screening questionnaire, with permission from the BRHS study group. It addressed in detail current and previous (lifelong) exposures under the following headings: occupational and economic status, patterns of physical activity, alcohol intake, smoking habits and use of medication, and family history of cardiovascular disease, hypertension, and diabetes mellitus. Smoking status was classified into three categories: never smoker, former smoker, and current smoker. Participants were divided by alcohol consumption into heavy drinkers (men $>$ 21 units a week and women $>$ 14 units a week), moderate drinkers (men who drank alcohol but drank $<$ 21 units a week and women who drank alcohol but drank $<$ 14 units a week), and non-drinkers. Social class was classified from current or former primary longest held occupation or by spouse's occupation for participants who gave no occupation or worked in the home. Social class was divided into nine occupational groupings according to standardised occupational coding lists from the Central Statistics Office of Ireland.[16] Both groups were measured for height, weight, and waist to hip ratio. These were measured by the same standardised methods used in the Cork and Kerry study.[17]

Measurement of chronic infections

H pylori antibody status was tested in the microbiology laboratory in the Mercy Hospital, Cork, with the Biomaster Assay Junior. The assay used was the Premier *H pylori* assay kit (Meridian Bioscience Inc, Cincinnati, Ohio, USA). This assay has a sensitivity of 88% and a specificity of 96%.[18] Serum was tested for cytomegalovirus infection with the Biotest anti-human cytomegalovirus recombinant IgG enzyme linked immunosorbent assay (ELISA) in the National Virus Reference Laboratory, University College Dublin. The Biotest IgG ELISA has a sensitivity of 100% and a specificity of 99%.

C pneumoniae antibody status was measured in the Virus Reference Laboratory in University College Dublin with an ELISA. Antibody status to *C pneumoniae* was determined for IgA, IgM, and IgG antibodies. The antibodies were measured in enzyme immune units (EIU). For IgA antibodies a value of $>$ 12 EIU was treated as positive, a value of 8–12 EIU was equivocal, and a value of $<$ 8 EIU was negative. For IgG antibodies $>$ 45 EIU was positive, 30–45 EIU was equivocal, and $<$ 30 EIU was negative. For IgM $>$ 1.1 EIU was positive, 0.5–1.1 EIU was equivocal, and $<$ 0.5 was negative. For the purposes of the analysis equivocal results were regarded as negative. The Labsystems enzyme immunoassay has a sensitivity of 91% and 85% and specificity of 80% and 88% for IgG and IgA, respectively.

HSV types 1 and 2 were measured in the National Virus Reference Laboratory in University College Dublin with the Diamedix enzyme immunoassay (Diamedix, Miami, Florida, USA). The Diamedix enzyme immunoassay has a sensitivity of 100% and a specificity of 92.7%.[19]

Statistical analysis

The data were entered on to an OmniForm database (ScanSoft, Peabody, Massachusetts, USA) and analysed with Minitab for Windows (version 13; Minitab, State College, Pennsylvania, USA) and SAS version 10 (SAS Institute, Cary, North Carolina, USA). Adjusted means were compared by the analysis of variance-general linear model function on Minitab. Proportions were compared by χ^2 tests. Matched and unmatched analyses were conducted by, respectively, unconditional and conditional logistic regression. Odds ratios were calculated as the estimate of association. The results of the analyses were similar; therefore, only the unmatched analyses are reported here.

Ethics

The study complies with the Declaration of Helsinki. Patients gave informed consent for the study, which has been

Table 2 Seropositivity for *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, and herpes simplex virus types 1 and 2 in patients and controls

Antibody response	Patients (n = 227)	Controls (n = 277)	p Value
C pneumoniae (IgG)	117 (52.0)	136 (50.6)	0.20
C pneumoniae (IgA)	122 (54.2)	136 (50.7)	0.44
C pneumoniae (IgM)	8 (1.8)	15 (1.5)	0.29
H pylori (IgG)	139 (62.3)	162 (61.4)	0.80
Cytomegalovirus (IgG)	103 (45.8)	104 (38.7)	0.10
Herpes simplex (IgG)	207 (92.0)	243 (90.3)	0.50

n (%).

Table 1 Baseline physical characteristics of patients and controls

Variable	Patients (n = 227)	Controls (n = 277)	p Value
Age (years)	59.4 (58.2 to 60.7)	59.0 (57.9 to 60.1)	0.63
Height (cm)	168.2 (167.1 to 169.4)	170.0 (169.1 to 171.0)	0.02
Weight (kg)	79.6 (77.7 to 81.6)	79.0 (77.5 to 80.5)	0.60
BMI (kg/m^2)	28.1 (27.5 to 28.6)	27.3 (26.8 to 27.7)	0.04
Waist circumference (cm)	97.5 (95.9 to 99.2)	94.4 (93.0 to 95.8)	0.01
Hip circumference (cm)	102.3 (100.9 to 103.6)	104.6 (103.7 to 105.4)	0.01
Waist to hip ratio	0.95 (0.95 to 0.95)	0.90 (0.89 to 0.91)	<0.01
Men	162 (71.4%)	208 (75.1%)	0.35
Current smokers	81 (36.2%)	45 (16.2%)	<0.01
Heavy drinkers	39 (18.1%)	24 (9.8%)	<0.01
Social class 1+2	24 (10.6%)	46 (16.6%)	0.05
Self reported hypertension	59 (26.0%)	82 (29.6%)	0.04
Self reported diabetes mellitus	7 (3.1%)	5 (1.8%)	0.36
Family history of CVD	123 (57.5%)	113 (42.0%)	<0.01

Data are mean (95% confidence interval (CI)) or number (%).
BMI, body mass index; CVD, cardiovascular disease.

Table 3 Age and sex adjusted and fully adjusted odds ratios (OR) and 95% CI for acute coronary syndrome by seropositivity (IgG) to *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, and herpes simplex virus types 1 and 2 infections

Positive antibody response (IgG)	OR (age and sex adjusted)	OR (fully adjusted)
C pneumoniae	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)
H pylori	1.0 (0.9 to 1.1)	0.9 (0.8 to 1.0)
Cytomegalovirus	0.7 (0.5 to 1.1)	0.7 (0.5 to 1.1)
Herpes simplex	0.8 (0.4 to 1.5)	0.7 (0.3 to 1.5)

Adjusted for age, sex, smoking, social class, exercise, alcohol use, and waist to hip ratio.

considered and approved by the Cork Teaching Hospitals research ethics committee.

RESULTS

The 5C study achieved a response rate of 94% for patients (227 of 241 potential cases) and 73% for controls (277 out of 377). Table 1 summarises the main baseline cardiovascular risk factors for both groups. The majority of patients were men (71% *v* 29% women). The ages of patients and controls were similar (59.4 years *v* 59.0 years, p = 0.63), reflecting their matching. There was a significant difference in height with patients being shorter than controls, even after adjustment for age and sex (168.2 cm *v* 170.0 cm, p = 0.02). The weights of patients and controls were similar (79.6 kg *v* 79.0 kg, p = 0.60). There was a significant difference between patients and controls with regard to average body mass index (28.1 kg/m^2 *v* 27.3 kg/m^2, p = 0.04). There was also a highly significant difference between groups with regard to waist to hip ratio (0.95 *v* 0.90, p = 0.00). A higher proportion of patients were smokers, were heavy drinkers, and had a family history of cardiovascular disease (36.2% *v* 16.2%, p = 0.00; 18.1% *v* 9.8%, p = 0.01; and 57.5% *v* 42.0%, p = 0.00, respectively).

Table 2 outlines the proportion of patients and controls who were seropositive to *H pylori*, cytomegalovirus, HSV types 1 and 2, and *C pneumoniae*. There were no significant differences between patients and controls with regard to seropositivity to *H pylori* (60% *v* 61%), cytomegalovirus (46% *v* 39%), and HSV types 1 and 2 (92% *v* 90%). Both patients and controls had a similar serological response for all three classes of *C pneumoniae* antibody, with 54% of patients and 51% of controls being positive for IgA antibodies, 2% of patients and 1% of controls positive for IgM antibodies, and 52% of patients and 51% of controls positive for IgG antibodies.

Table 3 outlines the age and sex adjusted and fully adjusted (adjusted for age, sex, social class, waist to hip ratio, smoking, alcohol, and exercise) odds ratios for acute coronary syndrome by seropositivity (IgG) to *C pneumoniae*, *H pylori*, cytomegalovirus, and HSV types 1 and 2 infections. There was no evidence of an increased risk of acute coronary syndrome with any of the four infections. The age and sex adjusted and fully adjusted odds ratios of acute coronary syndrome for patients who were seropositive (by IgG antibodies) to *C pneumoniae* were both 1.0. Similar results were found for the association of acute coronary syndrome with IgA and IgM seropositivity to *C pneumoniae* infection. For *H pylori* the age and sex adjusted and fully adjusted odds ratios for acute coronary syndrome were 1.0 (95% confidence interval (CI) 0.9 to 1.1) and 0.9 (95% CI 0.8 to 1.0). The unadjusted odds ratio for acute coronary syndrome for cytomegalovirus and for HSV types 1 and 2 was 0.7 (95% CI 0.5 to 1.1) and 0.8 (95% CI 0.3 to 1.5), respectively. The adjusted odds ratios were similar, 0.7 (95% CI 0.5 to 1.1) and 0.7 (95% CI 0.3 to 1.5), for cytomegalovirus and HSV types 1 and 2, respectively.

Table 4 outlines the age and sex adjusted and fully adjusted odds ratios for acute coronary syndrome by increasing number of chronic infections (as defined by seropositivity (IgG) to *H pylori*, cytomegalovirus, HSV types 1 and 2, and *C pneumoniae*) compared with no chronic infection. There was no evidence of an increased risk of acute coronary syndrome with increasing number of chronic infections. The test for trend was also non-significant.

Table 4 Age and sex adjusted and fully adjusted OR and 95% CI for acute coronary syndrome by increasing number of chronic infections

Number of chronic infections	OR (age and sex adjusted)	OR (fully adjusted)
0	1.0	1.0
1	1.3 (0.3 to 6.3)	0.9 (0.1 to 6.9)
2	1.2 (0.3 to 5.4)	0.7 (0.1 to 5.0)
3	1.0 (0.2 to 4.6)	0.6 (0.1 to 4.5)
4	1.2 (0.2 to 5.6)	0.9 (0.1 to 6.5)

Adjusted for age, sex, smoking, social class, exercise, alcohol use, and waist to hip ratio

DISCUSSION

In this community based case–control study we found no evidence of an association between acute coronary syndrome and *C pneumoniae*, *H pylori*, cytomegalovirus, and HSV types 1 and 2 infections.

The findings with regard to the individual organisms are consistent with previous studies. A meta-analysis performed by Danesh and colleagues[6] in 2000 identified 15 prospective studies of *C pneumoniae* IgG titres and coronary heart disease. The partially adjusted odds ratio for coronary heart disease for all 15 studies combined was 1.19 (95% CI 0.99 to 1.41). Adjustment for adult and childhood socioeconomic status did not significantly alter the results. In a meta-analysis examining the association between cytomegalovirus infection and coronary heart disease, Danesh and colleagues[20] found no association between seropositivity to cytomegalovirus infection and coronary heart disease (odds ratio 0.91, 95% CI 0.69 to 1.19). The evidence to date on the association between *H pylori* infection and coronary heart disease has been inconclusive due to contradictory results from different studies.[21–23] Similarly no clear association between HSV infection and coronary heart disease has emerged.[24–26]

Several randomised controlled trials have investigated the effects of antimicrobial agents on the risk of recurrent coronary heart disease, including ROXIS (randomised trial of roxithromycin in non-Q-wave coronary syndromes), ACADEMIC (azithromycin in coronary artery disease: elimination of myocardial infection with chlamydia), ISAR-3 (intracoronary stenting and antithrombotic regimen 3), STAMINA (South Thames trial of antibiotics in myocardial infarction and unstable angina), and WIZARD (weekly intervention with Zithromax for atherosclerosis and its related disorders).[7 9 27–29] Overall in the trials antibiotics have not had a beneficial effect in the treatment of coronary heart disease.

Some studies have reported an association between number of infections and risk of coronary heart disease. Espinola-Klein and colleagues[30] assessed the impact of infectious burden on extent and long term prognosis of atherosclerosis and reported a positive association between increasing level of seropositivity to infection and risk of atherosclerosis. Zhu and colleagues[31] and Rupprecht and

associates[32] reported similar findings, though the numbers were small.

Conclusion

In this community based case–control study we found no association between *C pneumoniae*, *H pylori*, cytomegalovirus, and HSV types 1 and 2 infections and acute coronary syndrome. We also found no evidence of a burden of infection effect.

ACKNOWLEDGEMENTS

The authors acknowledge the Health Research Board and the Irish Heart Foundation for providing funding for this project.

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Conflicts of interest: None

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Intracerebral haematoma masquerading as ventricular standstill

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An 82 year old man was referred to the emergency room by his general practitioner for a right frontoparietal headache. The preceding day he had tripped and fallen, hitting the back of his head on the floor. Computed tomography showed a cortical contre coup haematoma. In view of ventricular standstill noted on ECG, a temporary pacing wire was inserted and a dual chamber permanent pacemaker was subsequently implanted. Intracerebral bleeding was treated conservatively and the patient made a good recovery. All patients admitted with head injury and sinus bradycardia or sinus arrest should be nursed at 15° to 30° with instructions to avoid the head up and supine positions. Furthermore, brain CT should be promptly recorded to assess for intracerebral haematoma and raised intracranial pressure and, if they are confirmed, these patients with cardiovascular compromise should benefit from close collaboration between neurosurgeon and cardiologist. Urgent pacing should be considered for all patients with head injury who experience symptomatic bradycardia or ventricular standstill.

(*Heart* 2005;**91**:e1) www.heartjnl.com/cgi/content/full/91/1/e1